Multi-Channel Transcutaneous Cortical Stimulation System

Contract # N01-NS-7-2365

Progress Report #14

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Introduction

The goal of this project is the design, fabrication, and testing of a ***Multi-Channel Transcutaneous Cortical Stimulation System*** to be used in a prototype artificial vision system**.** During the past 25 years, the development of a neuroprosthesis that could be used to restore visual sensory functions has been an important goal of the Neural Prosthesis Program (NPP) of the National Institute of Disorders and Stroke, National Institutes of Health. Demonstrations of the feasibility of a visual prosthesis have reached the stage in which the NPP is highly motivated to initiate the development of a fully implantable cortical stimulation system which could be used to provide inputs and computer control for hundreds, to over one thousand, implanted cortical electrodes. This is the fourteenth progress report for this project. In this report we consider the technological developments that have been accomplished, in this contract, and we present an assessment of the feasibility of using our implantable stimulator design in an intracortical visual prosthesis.

Status of the Implantable Stimulation System

Electrical testing of the application specific integrated circuits, for the 256-implantable cortical stimulation system show that all aspects of the electronic circuitry function as expected. In our last progress report we described a test in which we connected an 8-channel block chip to a state machine chip, to a rectifier front-end chip. The input to the rectifier front –end chip was a wire-wound coil. The coil was coupled to a 5MHz transmitter over a distance of 1 cm. The transmitter was driven by a Labview interface Graphical User Interface (GUI). The Labview GUI allowed commands to be sent, via the inductive link to the "implant" circuitry. The digital stream was properly decoded, and the appropriate electrode channel was controlled. This important test demonstrates the feasibility of using the IIT-designed circuitry as a stimulator module, and more importantly tests the operation of the exact physical configuration of this circuitry, as implemented in silicon chips.

Packaging of the 256-channel implantable stimulation system relies upon the use of a high-density multi-chip modules, that incorporate a packaging density which is roughly 10 times that of industry standards. This is accomplished using machinable ceramic and matched-temperature-coefficient glass seals. Our saline soak tests, performed over the past two years, show no evidence of water infiltration into the sealed test modules. Conventional helium leak testing has revealed an anomaly of the machinable ceramic: the bulk material absorbs helium in surface imperfections, then releases the helium during subsequent testing in the leak detector. We are addressing this issue, by investigating the nature of the surface defects that contribute to this behavior, as well as by using humidity sensitive test patterns, within sealed packages to directly measure the moisture ingress. It is our feeling, that this is more of a measurement issue related to the helium leak testing rather than a genuine problem of moisture ingress. We anticipate qualifying this sealing, and packaging method, in the first quarter of 2001. Based on this packaging technology we plan to adapt the geometric configuration of the 256-channel module according to surgical considerations.

In summary, we see no technological obstacles the use of the basic technology, developed under this contract, in specifying and fabricating a 256-channel cortical stimulator suitable for use in an intra-cortical visual prosthesis.

Status of Electrode Designs and Configurations

The 1996 study by Schmidt, et. al, used electrodes that were inserted by hand forceps, individually, and in pairs. This method was adequate for the 38 electrodes used in that study, and may be adaptable to a somewhat larger number of electrodes. However, as the desired number of electrodes approaches 1000, or more, there is some question as to the feasibility of implanting a large number of intracortical electrodes by hand. Work done at Huntington Medical Research Institute, and funded by NINDS, has demonstrated the possibility of using 16-electrode tiles as an alternative. These tiles would facilitate the implantation of over 1000 electrodes through the use of a high-speed injector. Researchers at Huntington have demonstrated that by using insertion speeds of up to 1M/sec, minimal bleeding and tissue damage, caused by the insertion, result. These encouraging results suggest that a combination of hand-inserted electrodes, and high-speed inserted tiles provide a feasible mechanism to blanket Area V1 with an equally-spaced array of electrodes. Therefore, from a purely mechanical standpoint, we feel that is it feasible to surgically implant approximately 1000 electrodes into the primary visual cortex of a human.

Expectations of Threshold Stability of Implanted Electrodes

Based upon the 1996, NIH Study by Schmidt, et al, and subsequent work at Huntington Medical Research Institute, and EIC Laboratories, it is likely that a sufficient number of implanted electrodes would have stimulus amplitude and pulse-width thresholds that are within the safe charge limits for activated iridium oxide. Questions remain as to the long-term reliability of these electrode-neural interfaces. Testing needs to be performed, over a period of months, to years, that raise our confidence concerning the maintenance of the electrode-tissue interface, and the stability of psycho-physical percepts invoked by the stimulation.

Animal Models for Studying Intra-cortical Stimulation

The use of animal models for investigating, and estimating, the likely functionality of an intra-cortical visual prosthesis is debatable. The success of such models, particularly using non-human primates, depends upon the ability of the researcher to measure what the animal perceives. This is not an easy task, however in recent years novel methods have been developed that allow for the determination of the animal's response to visual as well as electrically-induced perception. It is our assessment that an animal model is highly desirable. An electrical stimulation system can be tested in a sighted animal, thus allowing for direct comparison between visual stimuli and electrical stimuli. Such testing could not be performed in a human, and could be invaluable in helping to determine stimulation strategies for the human. Our concern is that without systematic testing of stimulation strategies, using thousands, to hundreds of thousands of trials, key image-to-stimulus transformations may be precluded by the system design, and the options for discovering optimal stimulation strategies, in the human, may be seriously limited. Due to the small number of, and the short duration of, human-based experiments, stimulation data are scarce, studies have been largely qualitative, and observations largely anecdotal. We believe that a visual prosthesis will not be effective until ways have been found to study them rigorously, and until we can develop a logical, physiologically-oriented approach to their application.

Possible Strategies for Animal Testing

Below, we propose a set of possible animal tests that might be used in developing an animal model for visual prosthesis evaluation. The most compelling question to consider, when planning experiments for visual prostheses, is the question of suitable *algorithms* for manipulating vision through parallel electrical stimulation.

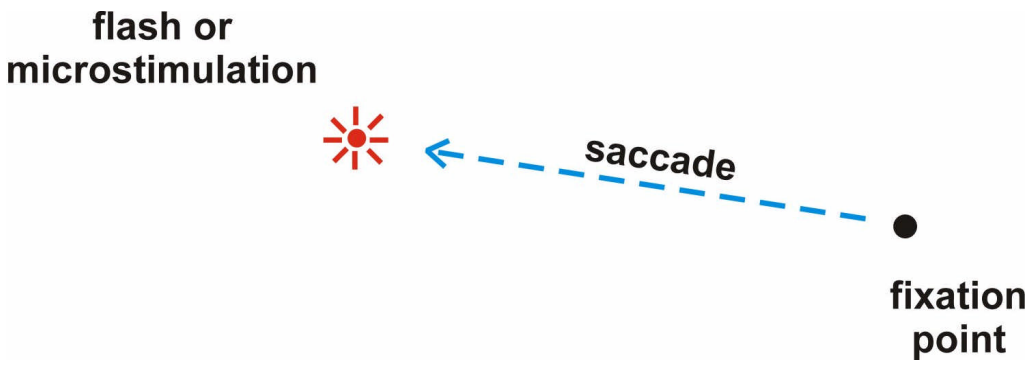
The idea is: assuming an electrically-functional prosthesis, how can we use it most effectively to recreate vision? One possible approach is to develop techniques in an animal model that will permit testing of many different strategies quickly and thoroughly (neither of which is possible with humans). Specific short-term aims might be:

1) Develop a behavioral assay for the rapid and precise evaluation of stimulation protocols. By testing stimulation parameters in a setting where literally hundreds of thousands of trials can be performed per year, one could not only fine-tune stimulation parameters (current, frequency, etc) but also explore novel ways of organizing current pulses (e.g. poisson-distributed, clustered).

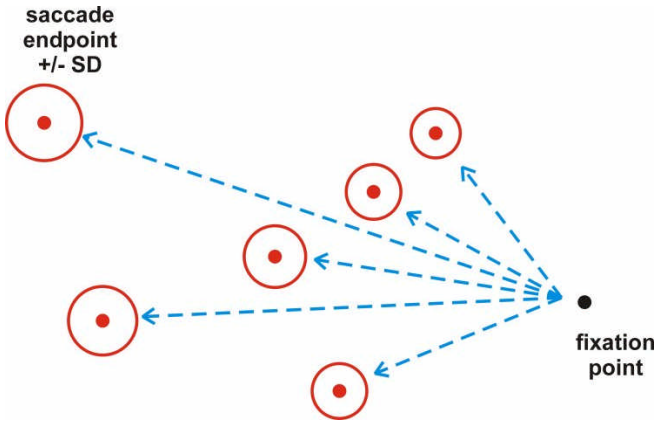
2) Evaluate the potential for tuned-response manipulation. It has been demonstrated that phosphene percepts can be evoked in humans, consistently signaling a given location in the visual field. A potential long-term strategy might therefore be to maximize the resolution with which phosphenes can be induced, with the goal of delivering visual information in the form of pixellated images (scoreboard strategy). However a potentially far more effective strategy would involve the selective activation of neurons according to their tuning properties (tuned-response strategy). For example, one might transmit information about objects by activating neurons whose orientation preferences trace out the object's shape, as opposed to rendering the entire object as a texture map. This is a good idea in principle, but no one knows if it is feasible. This approach warrants further investigation.

Experiments for Aim 1 (Saccade task)

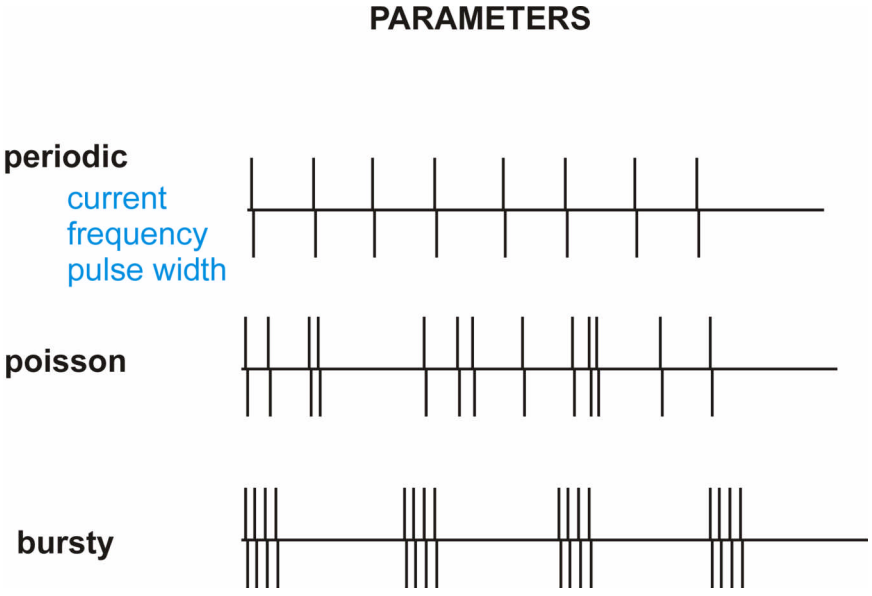
Monkeys will learn to fixate, then saccade to (look at) a small flash in the visual field. Saccade targets will initially be visual, but later the flash will be induced by stimulating a particular electrode site. Visual targets will gradually decrease in number and luminance, while stimulated targets increase in current and number. Eventually monkeys are expected to saccade consistently to stimulated targets.



The effectiveness of stimulation can be evaluated in terms of the standard deviation around each saccade. Note that this task would not be possible with a single electrode, since monkeys would quickly memorize the target location. With many electrodes, activated randomly, the monkey must continually saccade to the location he perceived an instant before.



This "behavioral assay" will allow rapid and robust testing of stimulation protocols. For traditional, periodic stimulation, optimal combinations of current, frequency and pulse-width will be found. We also propose testing random vs. periodic temporal patterns: since neurons are know to discharge randomly (not periodically), it is logical to ask whether stimulation pulses are more effective when delivered with random timing.

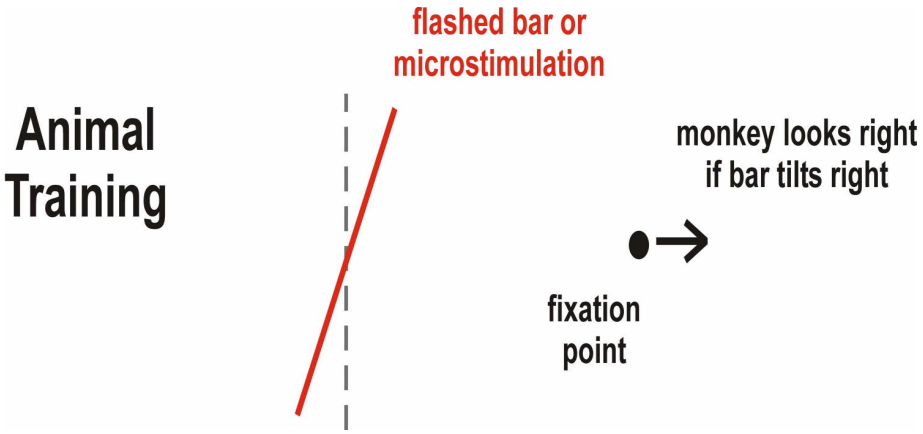


Finally, we propose testing various degrees of "burstiness." Some physiological studies suggest that information is encoded in the tendency of spikes to cluster in time. Again, it is reasonable to ask whether this could be an effective stimulation strategy.

Experiments for Aim 2 (Orientation task).

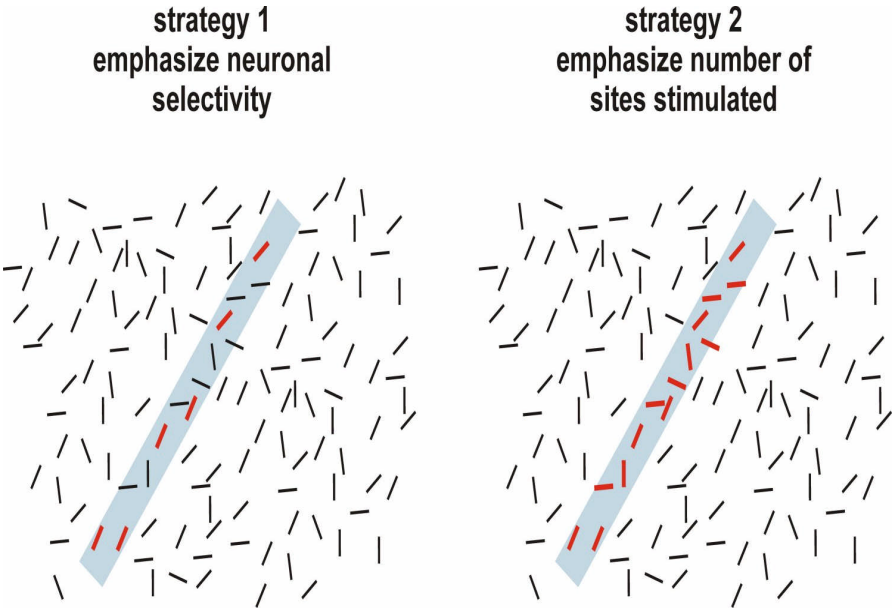
Monkeys will fixate while an oriented bar is briefly flashed. Monkeys will then look right if the top of the bar tilted right of vertical, left if the top of the bar tilted left of vertical.

Flashed bars will gradually be replaced with stimulated bars, which will be produced in one of two ways.



1) An imaginary rectangular window will be placed over the receptive fields of the neurons accessible at the stimulation sites. All neurons whose receptive field falls within the window, and whose orientation preference roughly matches the orientation of the rectangular window, will be activated. The imaginary window will assume one of 8 different orientations, in random order.

2) Same as (1), except that *every* neuron whose receptive field falls within the bar will be activated.



The response variable is the sensitivity in the task (defined as the minimum angle from vertical required to get 75% correct answers or better). Since the number of neurons activated in strategy (1), as a fraction of the number stimulated in strategy (2), will vary, we can plot the threshold as a function of this ratio. We hypothesize that the lowest threshold will occur for a ratio less than 1; that is, orientation percepts are elicited more precisely when neuronal selectivity is emphasized over the total number of neurons activated.

The issue of whether such studies can be successful has proponents and opponents. There are some previous studies that suggest the feasibility of the proposed experiments:

[1] Britten, K.H. and van Wezel, R.J., Electrical microstimulation of cortical area MST biases hading perception in monkeys, Nat Neurosci, 1 (1998) 59-63.

Here Britten used microstimulation in monkeys to induce a sense of heading.

[2] DeAngelis, G.C., Cumming, B.G. and Newsome, W.T., Cortical area MT and the perception of stereoscopic depth, Nature, 394 (1998) 677-80.

Deangelis used microstimulation in MT to induce a sense of depth.

[3] Salzman, C.D. and Newsome, W.T., Neural mechanisms for forming a perceptual decision, Science, 264 (1994) 231-7.

Salzman used stimulation in MT to induce a sense of direction.

All three of the above resemble our proposed studies in that they are based on ambiguous perceptual tasks (we don't know a priori what the monkey perceives). It seems likely that such ambiguous tasks can be highly controlled, basically using statistical inference.

These studies and our proposed ones also have in common, that monkeys reported a featural percept (heading, direction, depth) induced by microstimulation.

The differences are that 1) they used a single electrode, and 2) they measured stimulation effects through biases, rather than directly (but the latter should be possible with multiple electrodes).

Summary

In summary, we feel that that the fundamental technologies for fabrication of a 1000-channel intra-cortical stimulation system exist, and that they are adaptable to a specific implantable device design. Such as system could be used to perform key animal experiments related to safety and efficacy of a cortical visual prosthesis. This effort would need to be approached by a multi-disciplinary team dedicated to the development and implementation of a human visual prosthesis.